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Iterative catalyst controlled diastereodivergent synthesis of polypropionates†‡

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D. Roke,[a] M. Fañanás-Mastral*[a,b] and B. L. Feringa*[,a]

Polypropionate fragments are synthesized using a combination of a copper-catalyzed asymmetric allylic alkylation, ruthenium-catalyzed cross-metathesis and an iridium-catalyzed asymmetric allylic etherification. The use of the appropriate chiral ligand for each catalytic reaction allows access to 1,2-hydroxymethyl arrays with good to excellent control over the relative and absolute configuration of the different stereocenters.

Introduction

Polypropionates are important subunits in many polyketides, one of the major classes of natural products featuring a wide range of biological activities (Figure 1).[1,2] In pharmaceutics, polyketides have also found various applications, being used as antibiotics, immunosuppressants, antiparasitics, cholesterol lowering drugs, and antitumor agents.[3]

Polypropionates consist of alternating methyl- and hydroxyl-substituted stereocenters. The combination of these two different motifs lead to a large number of possible distinct stereochemical combinations. The importance of these complex chemical structures has directed a lot of attention towards the diastereoselective and enantioselective synthesis of polypropionates.[4] In an attempt to mimic the biosynthetic pathway, the stereoselective aldol reaction is arguably the most extensively studied method.[5,6] However, a large number of highly successful alternative approaches has been reported such as crotylations,[7] reductive aldol couplings[8] and epoxide ring-opening reactions.[9] Important methods for the asymmetric synthesis of polypropionates frequently start with stoichiometric amounts of chiral material, either from natural sources or often in the form of chiral auxiliaries which are to be attached and cleaved off in separate steps.

A growing number of catalytic methods towards polypropionates is emerging,[4] and examples include (organo)catalytic aldol couplings,[5,10] reductive aldol couplings[4,8,11] and catalytic crotylations.[12] Although already a variety of useful catalytic asymmetric methods towards chiral propionate units exists, most of these methods are limited so far that only one 1,2-hydroxymethyl moiety is introduced,[10-12] making it difficult to perform these methods iteratively to allow the formation of polypropionates.

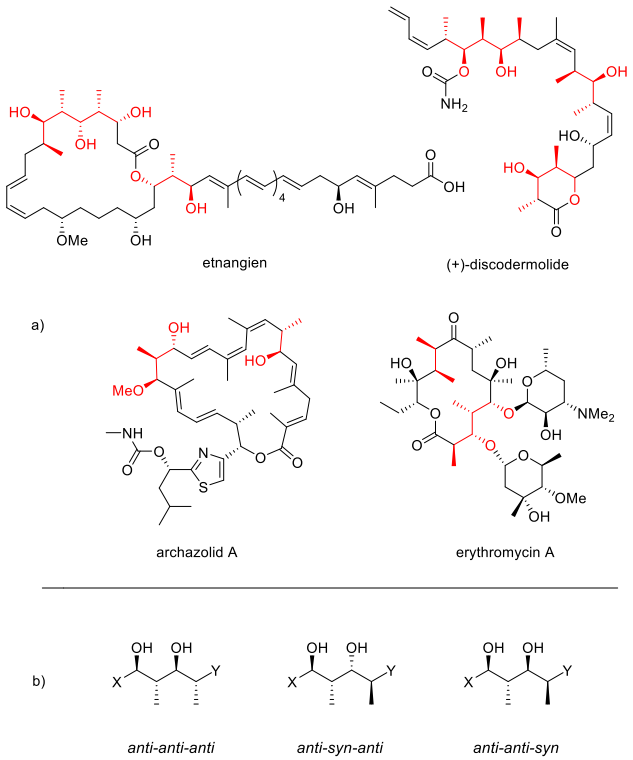

Figure 1: a) Examples of polyketides bearing polypropionate segments (highlighted in red). b) Three configurations of polypropionate segments described in this paper.

The transition metal-catalyzed asymmetric allylic substitution is a widely investigated reaction, which allows the formation of C-C, C-H, C-S, C-N and C-O bonds in a highly enantioselective manner.[13] In particular, the S_N2'-selective allylic substitution provides a versatile substrate which bears a stereocenter next

[a] Stratingh Institute for Chemistry, University of Groningen, Nijenborg 4, 9747 AG Groningen.
Email: B.L.Feringa@rug.nl
[b] Present address: Center for Research in Biological Chemistry and Molecular Materials (CIQUS) and Department of Organic Chemistry, University of Santiago de Compostela, 15782 Santiago de Compostela, Spain.
Email: martin.fananas@usc.es

†Dedicated to Prof. Barry Trost on the occasion of his 75th birthday

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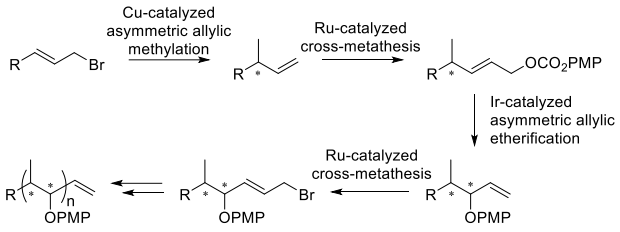
to a double bond which can be further functionalized.[13,14] Copper-catalyzed asymmetric allylic alkylations with organometallic reagents usually proceeds with high S_N2' selectivity being a powerful tool for the construction of optically active carbon stereocenters.[15] A wide range of chiral ligands has been utilized for the copper-catalyzed asymmetric allylic alkylation, examples include phosphoramidites,[16] diphosphine,[17] phosphine-phosphite[18] and NHC ligands.[19] Among these different catalytic systems, the combination of CuBr·SMe_2 with TaniaPhos **L1** has emerged as an excellent catalyst for the introduction of the methyl unit via copper-catalyzed AAA.[17]

On the other hand different transition metals have been employed for the asymmetric allylic C-O bond formation towards branched allyl ethers and alcohols.[20-28] Among these systems Ir/phosphoramidite complexes have emerged as very efficient catalysts for the S_N2'-selective asymmetric allylic etherification.[13d,f,g,23-27] Substitutions with phenoxides[23] and alkoxides[24a,b] and alcohols[24c] have been shown to provide excellent results. Moreover silanoates[25] and caboxylates[26] can be introduced and even a direct hydroxylation using carbonates as pronucleophiles has been reported.[27]

An iterative approach in which the methyl and hydroxyl substituents are introduced in separate allylic substitution steps, could be a potentially powerful approach towards polypropionates. A related strategy has been used before for the synthesis of 1,2-dihydroxy arrays[23e,28] and, albeit non-iteratively, for 1,2-aminoethyl arrays.[29] However for polypropionates only a few sequential approaches have been published,[30] and to the best of our knowledge a catalytic iterative approach in which alternating methyl and hydroxyl groups are sequentially introduced to arrive at the distinct diastereomers and enantiomers of polypropionates has not been reported.[4] A distinct advantage of such a catalytic iterative approach is that it can be performed in a diastereodivergent way, in which the diastereoselectivity is controlled fully by the chiral catalyst.

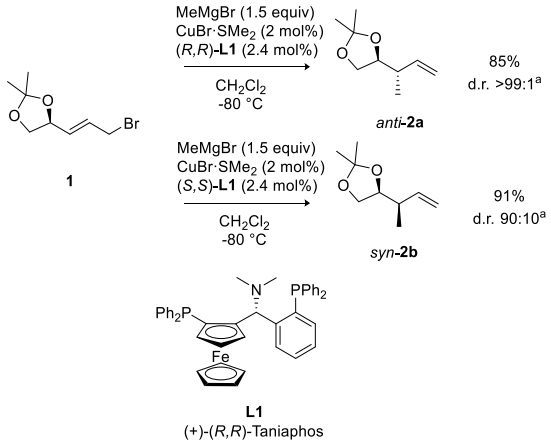


Scheme 1: Iterative catalytic approach towards polypropionates.

Herein we present an iterative catalytic method for the synthesis of polypropionates in which stereocenters are sequentially generated using a copper-catalyzed asymmetric allylic alkylation, reported earlier by our group,[17f] in combination with an iridium-catalyzed asymmetric allylic etherification (Scheme 1).[23d,e] The combination of subsequent asymmetric allylic substitution reactions allows for the sequential introduction of methyl- and hydroxyl-substituted stereocenters. Control over the distinct configurations was achieved by the use of the appropriate enantiomer of the chiral ligand to obtain the desired stereochemistry. After each new stereocenter that is introduced by a catalytic allylic substitution, a ruthenium-catalyzed cross-metathesis is performed to introduce either an allylic carbonate or allylic bromide to allow the next stereocenter to be introduced.

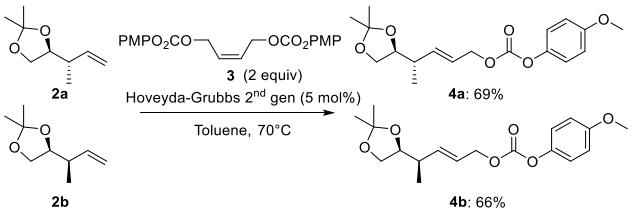
Results and discussion

Starting with acetal protected allyl bromide **1**, the first copper-catalyzed asymmetric allylic alkylation with MeMgBr was carried out using a Cu-Taniaphos catalyst to provide product **2** with high levels of stereocontrol (*anti* d.r. > 99:1; *syn* d.r. = 90:10, Scheme 2).[17f] Both *syn*- and *anti*-isomers of product **2** can be obtained by choosing the appropriate enantiomer of the Taniaphos ligand **L1**. Pure *syn*-**2b** diastereomer was readily obtained by column chromatography. The configuration of the newly formed stereocenter is determined largely by the chiral catalyst, rather than the chirality present in the substrate, indicating a high level of catalyst control. Protecting the adjacent allylic hydroxyl using a dioxolane ring appeared to be essential, since other protecting groups gave rather low conversion and/or regioselectivity.[17f]

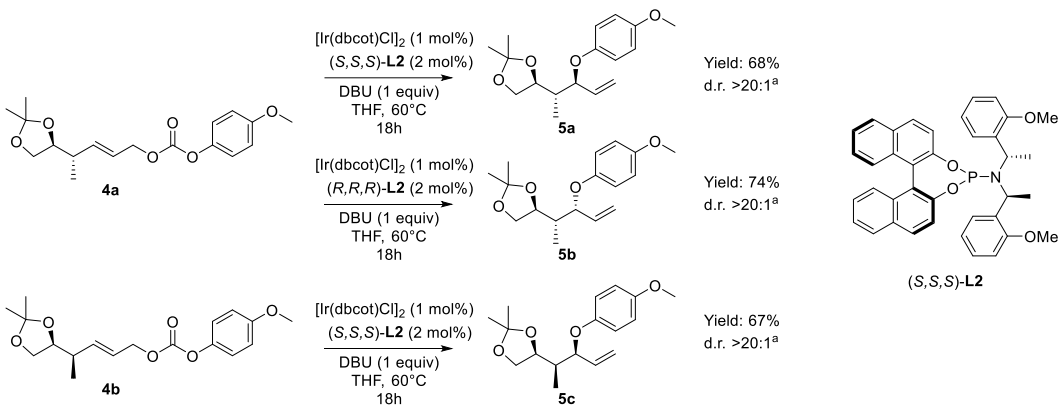


Scheme 2: Asymmetric allylic alkylations of allyl bromide **1** towards products **2**. [a]Diastereomeric ratio (d.r.) determined by GC-MS analysis.

Next, both *anti*- and *syn*-products **2** were converted into the corresponding allyl carbonates **4** by a cross-metathesis reaction. Using Hoveyda-Grubbs 2nd generation catalyst and the readily available (*Z*)-but-2-ene-1,4-diyl bis(4-methoxyphenyl) dicarbonate (**3**, Scheme 3), carbonates **4a** and **4b** were obtained in 69% and 66% yield, respectively.



Scheme 3: Cross-metathesis of anti- and syn-products **2** towards allyl carbonates **4**.

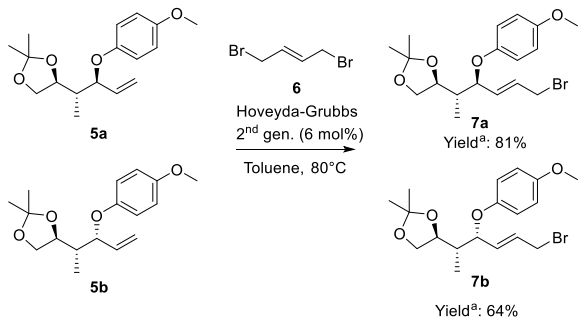


Scheme 4: Asymmetric allylic etherifications of allyl carbonates **4** forming allyl ethers **5**. [a]Diastereomeric ratio determined by GC-MS and ^{1}H-NMR analysis of the crude product.

In the next step we explored the iridium-catalyzed asymmetric allylic etherification arriving at products **5** bearing a 1,3-hydroxy-2-methyl unit, featuring three contiguous stereocenters (Scheme 4). A wide range of different methods for asymmetric allylic alkylations using O-nucleophiles have been reported, often giving rise to allylic ethers with excellent regio- and enantioselectivity.[20-21,23-27] Our attention was drawn by one specific method reported by Han and coworkers, in which a decarboxylative allylic etherification was performed, to provide branched allylic para-methoxyphenyl ethers (-OPMP).[23d,e] In contrast to the previous asymmetric allylic etherifications, this method does not require the use of an external nucleophile, leading to higher atom efficiency. Moreover, the para-methoxyphenyl ethers are generally easily cleaved under oxidative conditions to liberate the free hydroxyl moiety.[31]

Performing the etherification, using $[Ir(dbcot)Cl]_2$[32] in the presence of chiral phosphoramidite ligand **L2** and DBU as a base in THF (Scheme 4), resulted in high conversion towards the allylic ethers **5**. To our delight, when we applied Han's conditions to allylic carbonate **4a** with (*S,S,S*)-**L2**, *anti-anti* isomer **5a** was obtained with excellent diastereoselectivity. When the opposite enantiomer (*R,R,R*)-**L2** was used, substrate **4a** was converted into *anti-syn*-isomer **5b**. A diastereomeric ratio of over 20:1 was found, showing no obvious mismatch effect. Finally, when the asymmetric allylic etherification was performed on substrate **4b** using ligand (*S,S,S*)-**L2**, *syn-syn*-isomer **5c** was obtained, again with excellent control over diastereoselectivity, with a diastereomeric ratio of over 20:1. Moreover, in all cases, the control over regioselectivity is perfect, as no linear product due to S_N2 substitution was observed.

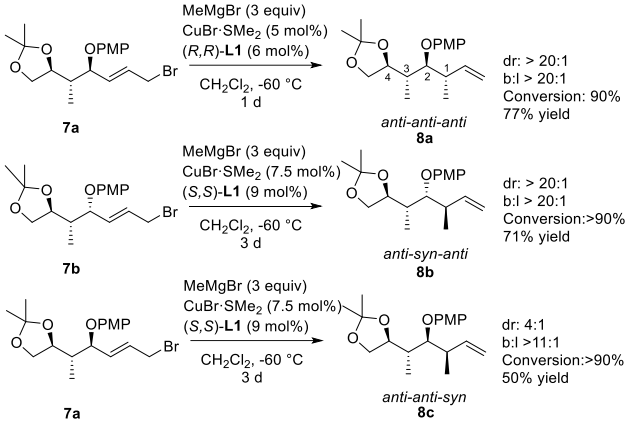
To highlight the potential iteration of our method, allyl bromides **7** were synthesized to perform a second copper-catalyzed asymmetric allylic alkylation. The terminal olefin was converted into the required allylic bromide necessary for the subsequent alkylation using a challenging cross-metathesis reaction (Scheme 5).[33] Substrates **5a** and **5b** were converted into the allylic bromides **7a** and **7b**, respectively, with (*E*)-1,4-dibromo-2-butene (**6**) applying Hoveyda-Grubbs 2nd generation catalyst. Allylic bromide **7a** and **7b** were obtained in 81% and 64% yield, respectively.[34]



Scheme 5: Cross-metathesis reactions to convert the terminal olefins into allylic bromides. [a]Yields are based on recovered starting material.

A second methyl substituent was introduced *via* a copper-catalyzed asymmetric allylic alkylation, creating a molecule bearing four consecutive stereocenters (Scheme 6). When we subjected substrates **7** to our previously optimized conditions for the copper-catalyzed asymmetric allylic alkylation of substrate **1**, high selectivity was obtained, but low rather conversion was observed. Therefore, a screening of temperatures, copper complexes and ligands was performed on a model substrate (see supporting information), showing that none of the tested systems gave better selectivity than our initial system consisting of $CuBr{\cdot}SMe_2$ and Taniaphos ligand **L1**. However, using this catalyst system, high conversion could be obtained by raising the temperature to -60 °C. When we subjected allylic bromide **7a** to these newly optimized conditions using (*R,R*)-Taniaphos **L1**, nearly full conversion and high selectivities in the allylic alkylation towards product **8a** bearing the *anti-anti-anti* configuration were obtained. This configuration has shown to be the most challenging stereochemical array to synthesize *via* conventional methods.[4d,35] Remarkably, the increase in temperature from -80 °C to -60 °C compared to the asymmetric allylic alkylation

of substrate **1** did not affect the S_N2':S_N2 ratio. Studies on copper-catalyzed asymmetric allylic alkylations on related structures bearing a vicinal stereocenter are very scarce. Notably, a recent study from our group showed that low regioselectivity is obtained with related substrates with other protecting groups at the allylic alcohol unit.[17f] Apart from this, as far as we know only a kinetic resolution of allylic substrates bearing an alkyl substituent at the allylic stereocenter has been published.[36]



Scheme 6[a,b]: Copper-catalyzed asymmetric allylic alkylation of allylic bromides **7**. [a]Branched to linear ratio, diastereomeric ratio and conversion were determined by ^{1}H-NMR analysis of the crude product. [b]For products **8b** and **8c**, after one day and with 5 mol% of copper, 30% and 50% conversion was obtained, respectively.

Product **8b** bearing *anti-syn-anti*-configuration was obtained with excellent selectivities and high conversion, although prolonged reaction times and increased catalyst loading are needed. Even though the configuration of the newly introduced substituent in product **8a** and **8b** are both *anti* with respect to the vicinal stereocenter, it is clear that the reaction towards product **8a** proceeds faster (1 d versus 3 d) and with lower catalyst loading (5 mol% versus 7.5 mol%). In this case it seems that the interaction with the more remote stereocenter (1,3-methyl-methyl interaction) has a rather large influence on the reactivity and that the 1,3-*syn*-configuration in product **8a** is preferred over the 1,3-*anti*-configuration in product **8b**. A similar effect was observed in the synthesis of deoxypropionates reported by Hanessian and coworkers and it was hypothesized that *syn*-pentane interactions[37] would be minimized in the Cu^{III}-intermediate when the methyl and Cu^{III}-complex are *syn* to each other, leading to the *syn*-product (Figure 2).[38] When these substituents are *anti* to each other (leading to *anti*-products), these interactions are maximized. It is however not clear what the effect of the bulky –OPMP substituent is and how this changes the 1,3-interaction.

The new protocol presented here was also effective for the even more challenging methylation towards the *anti-anti-syn*-**8c** stereoisomer. In this case, the methyl unit that had to be introduced is *syn* with respect to the vicinal stereocenter already present. As shown for substrate **1**, a mismatch effect is expected due to unfavorable steric interactions of the substrate with the catalyst when a methyl substituent is introduced with a 1,2-*syn*-configuration. Moreover, also the 1,3-methyl-methyl interactions are unfavorable, making this diastereomer the most difficult one to access. Despite the highly unfavorable interactions, high regioselectivity (b:l >11:1) was observed towards product 1,2-*syn*-**8c** when we subjected substrate **7a** to our reaction conditions, using (*S,S*)-Taniaphos **L1**. Although a slightly reduced stereoselectivity was observed in this case, most probably arising from competing substrate control, the *anti-anti-syn* isomer **8c** could still be obtained with good selectivity (dr = 4:1). It is important to note that the small amount of minor stereoisomer was readily removed by column chromatography to provide product **8c** as a single enantiomer in 50% yield.

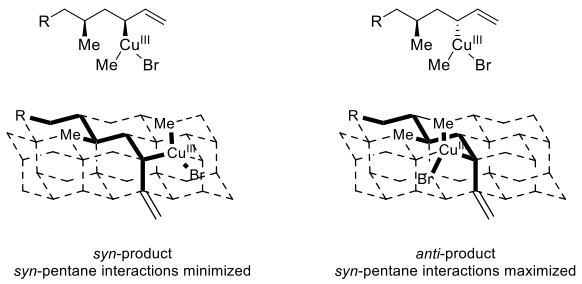
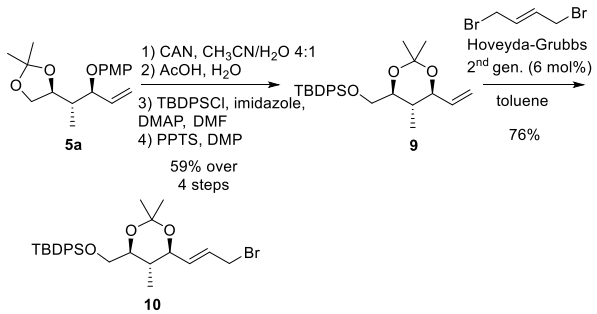


Figure 2: Syn-pentane interactions of 1,3-dimethyl moieties in a diamond lattice. Ligands on copper are not presented for clarification.

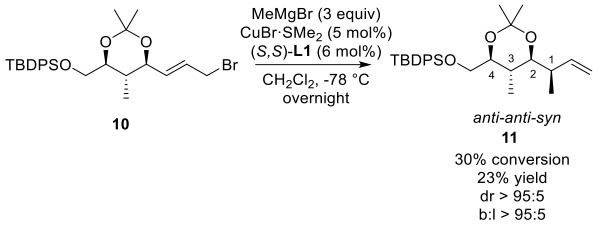
To overcome the mismatch effect observed on the allylic alkylation towards product *syn*-**8c** which resulted in a decrease in diastereoselectivity, an alternative approach was studied. In previous work, we showed that the presence of the dioxolane ring is essential to obtain high selectivity in an asymmetric allylic alkylation towards 1,2-hydroxymethyl units.[17f] We envisioned that installing a dioxane ring in our system might also improve the stereoselectivity. A sequence consisting of deprotection-protection steps starting from **5a** afforded olefin **9** in 59% overall yield (Scheme 7). Next, a ruthenium-catalyzed cross-metathesis was performed with (*E*)-1,4-dibromo-2-butene and Hoveyda-Grubbs 2nd generation catalyst to provide allylic bromide **10**.



Scheme 7: Synthesis of allylic bromide **10**.

This adapted strategy was highly rewarding as the copper-catalyzed asymmetric allylic alkylation on allylic bromide **10** shows that excellent stereoselectivity and regioselectivity are obtained towards product **11** (Scheme 8). Product **11** has the same *anti-anti-syn* configuration as product **8c**, but shows a near perfect degree of stereocontrol, likely due to the protection of the hydroxyl moiety as part of the dioxane ring.

Although this reaction suffers from rather low conversion, starting material can be readily recovered and resubmitted to the reaction. These results show that the three polypropionate segments bearing *anti-anti-anti*, *anti-syn-anti* and *anti-anti-syn* stereochemical units can be obtained in a catalytic iterative manner with branched linear and diastereomeric ratios of over 95:5.



Scheme 8: Copper-catalyzed asymmetric allylic alkylation towards product **11**. Conversion, diastereomeric ratio and branched to linear ratio are based on 1H-NMR analysis of the crude product.

Conclusions

In summary, a new method for the iterative catalyst controlled diastereodivergent synthesis of polypropionates is developed by combining a copper-catalyzed asymmetric allylic alkylation with a ruthenium-catalyzed cross-metathesis and an iridium-catalyzed asymmetric allylic etherification. Both methyl- and hydroxyl-substituted stereocenters are introduced with high regio- and diastereoselectivity. In each allylic substitution, despite the presence of (multiple) stereocenters, nearly full control over selectivity by the chiral catalyst is observed and the ability of synthesizing several diastereomers under catalyst control has been demonstrated with the preparation of *anti-anti-anti-*, *anti-syn-anti-* and *anti-anti-syn*-isomers. These synthetically valuable fragments can be accessed with excellent selectivities by the use of the appropriate enantiomer of the ligand in each catalytic reaction. Moreover, remarkably high selectivity towards the branched product was observed in the copper-catalyzed asymmetric allylic alkylation.

Acknowledgements

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Experimental section

Typical procedure for cross metathesis of olefins 2 with dicarbonate 3. In a Schlenk tube equipped with septum and stirring bar, Hoveyda-Grubbs 2nd generation catalyst (7.68 µmol, 4,81 mg), dicarbonate **3** (0.256 mmol, 99.4 mg) and olefin **2** (0.256 mmol, 40 mg) were dissolved in dry degassed toluene (2.5 mL) and stirred under nitrogen atmosphere at 70°C. After 5 h, a second portion of Hoveyda-Grubbs 2nd generation catalyst (5.20 µmol, 3.21 mg) and dicarbonate **3** (0.256 mmol, 99.4 mg) were added. After 18 h, water was added and the aqueous layer was extracted 3 times with CH_2Cl_2. The organic layers were combined and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography to yield the corresponding carbonate **4**.

(*S,E*)-4-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)pent-2-en-1-yl (4-methoxyphenyl) carbonate (4a) Purification by column chromatography (SiO_2 pentane/diethyl ether 3:1) afforded **4a** (65.5 mg, 69%) as a colorless oil. $[\alpha]_D^{20}$ = -2.4° (c = 1.0 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.09 (m, 2H), 6.88 (m, 2H), 5.91 (dd, *J* = 7.1, 15.6 Hz, 1 H) 5.71 (dt, *J* = 15.6, 6.5 Hz, 1H), 4.71 (m, 2H),3.99 (m, 2H), 3.80 (s, 3H), 3.63 (dd, *J* = 6.1, 13.3 Hz, 1H), 1.41 (s, 1H), 1.36 (s, 1H), 1.03 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 157.4, 153.9, 144.7, 138.4, 123.5, 121.9, 114.4, 109.1, 79.1, 69.1, 67.4, 55.6, 39.5, 26.5, 25.5, 15.6. HRMS (ESI+, *m/z*): Calcd for $C_{18}H_{25}O_6$ [M+H$^+$]: 337.1641, found: 337.1646.

(*R,E*)-4-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)pent-2-en-1-yl (4-methoxyphenyl) carbonate (4b) Purification by column chromatography (SiO_2 pentane/diethyl ether 3:1) afforded **4b** (136.9 mg, 66%) as a colorless oil. $[\alpha]_D^{20}$ = +15.2° (c = 1.0 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.09 (m, 2H), 6.88 (m, 2H), 5.74 (m, 2H), 4.67 (d, *J* = 5.3 Hz, 2H), 3.94 (m, 2H), 3.79 (s, 3H), 3.64 (m, 1H), 2.39 (m, 1H), 1.41 (s, 1H), 1.35 (s, 1H), 1.11 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 157.4, 153.9, 144.7, 137.8, 124.0, 121.8, 144.4, 109.1, 79.1, 68.9, 67.4, 55.6, 40.3, 26.7, 25.4, 16.2. HRMS (ESI+, *m/z*): Calcd for $C_{18}H_{25}O_6$ [M+H$^+$]: 337.1643, found: 337.1646.

Typical procedure for iridium-catalyzed allylic etherification of carbonates 4. In a Schlenk tube equipped with septum and stirring bar, $[Ir(dbcot)Cl]_2$ (4 µmol, 3.46 mg) and **L2** (8 µmol, 5.0 mg) were stirred for 10 min in THF (0.5 mL) under nitrogen atmosphere until a homogenous orange solution was obtained. DBU (0.2 mmol, 30 µmol) was added and the color changed to light yellow. Carbonate **4** (0.2 mmol, 67.3 mg) in THF (1.0 mL) was added and the mixture was stirred overnight at 60 °C. Water (1.5 ml) was added and the aqueous layer was extracted with Et_2O (3 x 1.5 ml). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography to yield compounds **5**.

(*S*)-4-((*2S,3S*)-3-(4-Methoxyphenoxy)pent-4-en-2-yl)-2,2-dimethyl-1,3-dioxolane (5a) Purification by column chromatography (SiO_2, pentane/diethyl ether 10:1) afforded **5a** (197.9 mg, 68%) as a colorless oil. $[\alpha]_D^{20}$ = -2.4° (c = 1.0 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.89 – 6.83 (m, 2H), 6.83 – 6.77 (m, 2H), 5.86 (ddd, *J* = 6.3, 10.7, 17.2 Hz, 1H), 5.31 (dd, *J* = 8.8, 14.0 Hz, 2H), 4.79 (dd, *J* = 4.8, 5.7 Hz, 1H), 4.06 – 3.98 (m, 2H), 3.76 (s, 3H), 3.72 – 3.65 (m, 1H), 2.27 – 2.15 (m, 1H), 1.41 (s, 3H) 1.36 (s, 3H), 0.93 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.8, 152.1, 134.8, 118.1, 117.1, 114.4, 108.6, 80.0, 76.6, 67.6, 55.7, 40.6, 26.7, 25.7, 10.1. HRMS (ESI+, *m/z*): Calcd for $C_{17}H_{25}O_4$ [M+H$^+$]: 293.1745, found: 293.1747.

(*S*)-4-((*2S,3R*)-3-(4-Methoxyphenoxy)pent-4-en-2-yl)-2,2-dimethyl-1,3-dioxolane (5b) Purification by column

chromatography (SiO_2, pentane/diethyl ether 10:1) afforded **5b** (217.2 mg, 74%) as a pale yellow oil. $[\alpha]_D^{20}$ = -2.8° (c = 1.0 in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 6.91 – 6.76 (m, 4H), 5.84 (ddd, *J* = 17.3, 10.7, 5.3 Hz, 1H), 5.27 – 5.20 (m, 2H), 4.85 – 4.81 (m, 1H), 4.17 (td, *J* = 7.9, 6.1 Hz, 1H), 4.02 (dd, *J* = 8.0, 6.0 Hz, 1H), 3.76 (s, 3H), 3.67 (t, *J* = 7.9 Hz, 1H), 1.95 – 1.86 (m, 1H), 1.41 (s, 3H), 1.32 (s, 3H), 0.96 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.9, 152.8, 136.8, 117.4, 116.6, 114.4, 108.5, 79.4, 77.0, 67.7, 55.7, 42.1, 26.7, 25.7, 8.7. HRMS (ESI+, *m/z*): Calcd for $C_{17}H_{25}O_4$ [M+H$^+$]: 293.1747, found: 293.1748.

(*S*)-4-((*2R,3S*)-3-(4-Methoxyphenoxy)pent-4-en-2-yl)-2,2-dimethyl-1,3-dioxolane (5c) Purification by column chromatography (SiO_2, pentane/diethyl ether 10:1) afforded **5c** (38.9 mg, 67%) as a colorless oil. $[\alpha]_D^{20}$ = +7.2° (c = 1.0 in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 6.84 – 6.77 (m, 4H), 5.89 – 5.79 (m, 1H), 5.29 – 5.22 (m, 2H), 4.50 (t, *J* = 5.1 Hz, 1H), 4.13 (dd, *J* = 13.8, 6.8 Hz, 1H), 4.04 (dd, *J* = 8.1, 6.0 Hz, 1H), 3.76 (t, *J* = 8 Hz, 1H), 3.75 (s, 3H), 2.03 – 1.95 (m, 1H), 1.37 (s, 3H), 1.35 (s, 3H), 1.13 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.9, 152.1, 135.7, 117.7, 117.0, 114.5, 105.3, 80.9, 77.1, 68.0, 55.6, 41.1, 26.6, 25.7, 11.4. HRMS (ESI+, *m/z*): Calcd for $C_{17}H_{25}O_4$ [M+H$^+$]: 293.1747, found: 293.1748.

Typical procedure for cross-metathesis of olefins 5 with (*E*)-1,4-dibromobut-2-ene. In a Schlenk tube equipped with septum and stirring bar, Hoveyda-Grubbs 2nd generation catalyst (0.015 mmol, 9.40 mg), (E)-1,4-dibromobut-2-ene (2.5 mmol, 577.3 mg) and olefin **5** (0.5 mmol, 146.2 mg) were dissolved in toluene (5 mL) and the mixture was stirred under nitrogen atmosphere at 80 °C. After 5 h, a second portion of Hoveyda-Grubbs 2nd generation catalyst (0.010 mmol, 6.27 mg) was added. After 18 h, water (4 ml) was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 3 ml). The combined organic layers were and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography to yield the corresponding allyl bromides **7**.

(*S*)-4-((*2S,3S,E*)-6-Bromo-3-(4-methoxyphenoxy)hex-4-en-2-yl)-2,2-dimethyl-1,3-dioxolane (7a) Purification by column chromatography (SiO_2, pentane/ethyl acetate 15:1) afforded **7a** (130.6 mg, 56%) as a pale yellow oil. $[\alpha]_D^{20}$ = +9.0° (c = 1.0 in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 6.86 – 6.78 (m, 4H), 6.00 (dt, *J* = 15.1, 7.5 Hz, 1H), 5.83 (dd, *J* = 15.4, 6.3 Hz, 1H), 4.87 – 4.83 (m, 1H), 4.04 (dd, *J* = 7.8, 6.0 Hz, 1H), 3.99 – 3.92 (m, 2H), 3.76 (s, 3H), 3.65 (dd, *J* = 9.9, 5.5 Hz, 1H), 2.26 – 2.17 (m, 1H), 1.41 (s, 3H), 1.37 (s, 3H), 0.92 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 154.0, 151.8, 132.0, 129.6, 117.1, 114.5, 108.8, 78.4, 76.6, 67.9, 55.7, 41.1, 31.8, 26.8, 25.7, 10.1. HRMS (ESI+, *m/z*): Calcd for $C_{18}H_{26}BrO_4$ [M+H$^+$]: 385.1009, found: 385.1002.

(*S*)-4-((*2S,3R,E*)-6-Bromo-3-(4-methoxyphenoxy)hex-4-en-2-yl)-2,2-dimethyl-1,3-dioxolane (7b) Purification by column chromatography (SiO_2, pentane/ethyl acetate 15:1) afforded **7b** (114.9 mg, 54%) as a pale yellow oil. $[\alpha]_D^{20}$ = -22.0° (c = 1.0 in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 6.89 – 6.77 (m, 1H), 5.90 (dt, *J* = 7.3, 6.8 Hz, 1H), 5.79 (dd, *J* = 15.4, 5.0 Hz, 1H), 4.89 – 4.86 (m, 1H), 4.14 (dt, *J* = 14.1, 7.1 Hz, 1H), 4.02 (dd, *J* = 8.0, 6.0 Hz, 1H), 3.95 (d, *J* = 7.3 Hz, 1H), 3.76 (s, 3H), 3.65 (t, *J* = 7.8 Hz, 1H), 1.93 – 1.84 (m, 1H), 1.41 (s, 3H), 1.31 (s, 3H), 0.95 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 154.1, 152.5, 134.1, 128.2, 117.4, 114.5, 108.6, 78.0, 76.9, 67.8, 55.7, 42.2, 31.9, 26.9, 25.7, 8.9. HRMS (ESI+, *m/z*): Calcd for $C_{18}H_{26}BrO_4$ [M+H$^+$]: 385.1009, found: 385.1002.

Typical procedure for asymmetric allylic alkylations of allylic bromides 7. In a Schlenk tube equipped with stirring bar and septum, CuBr·SMe_2 (0.010 mmol, 2.06 mg) and the corresponding ligand (0.012 mmol) were dissolved in CH_2Cl_2 (0.8 ml) and the mixture was stirred under nitrogen atmosphere at room temperature for 15 min. The mixture was cooled to -60 °C and MeMgBr (0.2 ml, 3M solution in Et_2O) was added dropwise. Allyl bromide **7** (0.2 mmol, 77.1 mg) was then added dropwise as a solution in CH_2Cl_2 (0.32 ml) over 1 h using a syringe pump. Once the addition was complete the resulting mixture was further stirred at -60 °C for 3 days. The reaction was quenched by addition of MeOH (0.2 ml) and the mixture was allowed to reach rt. Then, saturated aqueous NH_4Cl solution (2 ml) was added to the mixture. The organic phase was separated, and the resulting aqueous layer was extracted with CH_2Cl_2 (3 x 2 ml). The organic layers were combined and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography to yield the corresponding products **8**.

(*S*)-4-((*2S,3S,4S*)-3-(4-Methoxyphenoxy)-4-methylhex-5-en-2-yl)-2,2-dimethyl-1,3-dioxolane (8a) Purification by column chromatography (SiO_2, pentane/ethyl acetate 15:1) afforded **8a** (48.9 mg, 77%) as a colorless oil. $[\alpha]_D^{20}$ = +23.4° (c = 1.0 in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 6.88 – 6.77 (m, 4H), 6.01 – 5.91 (m, 1H), 5.07 (d, *J* = 16.9 Hz, 1H), 5.01 (dd, *J* = 10.3, 1.0 Hz, 1H), 4.31 (dd, *J* = 13.9, 6.3 Hz, 1H), 4.08 (t, *J* = 5.2 Hz, 1H), 3.89 (dd, *J* = 8.1, 6.3 Hz, 1H), 3.76 (s, 3H), 3.63 (t, *J* = 7.9 Hz, 1H), 2.73 – 2.63 (m, 1H), 2.34 – 2.24 (m, 1H), 1.40 (s, 3H), 1.34 (s, 3H), 1.11 (d, *J* = 6.9 Hz, 3H), 0.92 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.6, 153.5, 140.7, 116.6, 114.7, 114.6, 114.6, 108.2, 83.5, 76.1, 66.6, 56.7, 40.3, 38.2, 26.5, 25.4, 17.9, 11.3. HRMS (ESI+, *m/z*): Calcd for $C_{19}H_{28}O_4Na$ [M+Na$^+$]: 343.1880, found: 343.1880

(*S*)-4-((*2S,3R,4R*)-3-(4-Methoxyphenoxy)-4-methylhex-5-en-2-yl)-2,2-dimethyl-1,3-dioxolane (8b) Purification by column chromatography (SiO_2, pentane/ethyl acetate 15:1) afforded **8b** (48.9 mg, 77%) as a colorless oil. $[\alpha]_D^{20}$ = +2.2° (c = 1.0 in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 6.98 – 6.92 (m, 2H), 6.79 – 6.74 (m, 2H), 5.80 (ddd, *J* = 17.6, 10.3, 7.5 Hz, 1H), 5.06 (dd, *J* = 17.2, 1.2 Hz, 1H), 4.93 (d, *J* = 10.3 Hz, 1H), 4.34 (dd, *J* = 8.3, 1.8 Hz, 1H), 3.99 – 3.91 (m, 2H), 3.75 (s, 3H), 3.58 – 3.52 (m, 1H), 2.63 – 2.53 (m, 1H), 2.00 – 1.91 (m, 1H), 1.40 (s, 3H), 1.24 (s, 3H), 1.02 (d, *J* = 6.9 Hz, 3H), 0.94 (d, *J* = 6.9, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 154.3, 153.4, 141.4, 117.2, 114.5, 114.3, 108.6, 81.8, 77.2, 68.5, 55.7, 40.8, 39.3, 27.0, 25.6, 16.6, 9.1. HRMS (ESI+, *m/z*): Calcd for $C_{19}H_{28}O_4Na$ [M+Na$^+$]: 343.1880, found: 343.1879.

(*S*)-4-((2*S*,3*S*,4*R*)-3-(4-Methoxyphenoxy)-4-methylhex-5-en-2-yl)-2,2-dimethyl-1,3-dioxolane (8c) Purification by column chromatography (SiO_2, pentane/ethyl acetate 15:1) afforded **8c** (17.9 mg, 50%) as a colorless oil. $[\alpha]_D^{20}$ = -2.4° (c = 1.0 in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 6.90 – 6.83 (m, 2H), 6.82 – 6.77 (m, 2H), 5.82 (ddd, *J* = 17.4, 10.2, 8.6 Hz, 1H), 5.12 (dd, *J* =

17.6, 1.6 Hz, 1H), 5.03 (dd, *J* = 10.3, 1.7 Hz, 1H), 4.30 (q, *J* = 7.1 Hz, 1H), 4.14 (dd, *J* = 8.2, 3.4 Hz, 1H), 3.95 (dd, *J* = 8.1, 6.1 Hz, 1H), 3.76 (s, 2H), 3.58 (t, *J* = 8.0 Hz, 1H), 2.69 (h, *J* = 7.2 Hz, 1H), 2.25 (td, *J* = 7.0, 3.4 Hz, 1H), 1.40 (s, 3H), 1.36 (s, 3H), 1.09 (d, *J* = 6.7 Hz, 3H), 0.92 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.6, 153.4, 141.1, 116.5, 115.0, 114.6, 108.2, 82.8, 76.1, 67.4, 55.7, 41.0, 38.6, 26.5, 25.6, 17.7, 11.3. HRMS (ESI+, *m/z*): Calcd for $C_{19}H_{28}O_4Na$ [M+Na$^+$]: 343.1880, found: 343.1881.

(((*4S,5S,6S*)-6-((*R*)-But-3-en-2-yl)-2,2,5-trimethyl-1,3-dioxan-4-yl)methoxy)(tert-butyl)diphenylsilane (11) In a Schlenk tube equipped with stirring bar and septum, $CuBr{\cdot}SMe_2$ (0.0050 mmol, 1.00 mg) and (*S,S*)-**L1** (0.0060 mmol, 4.13 mg) were dissolved in CH_2Cl_2 (1.0 ml) and the mixture was stirred under nitrogen atmosphere at room temperature for 15 min. The mixture was cooled to -78 °C and MeMgBr (0.1 ml, 3M solution in Et_2O) was added dropwise. Allylic bromide **10** (0.1 mmol, 51.8 mg) was then added dropwise as a solution in CH_2Cl_2 (0.5 ml) over 1 h using a syringe pump. Once the addition was complete the resulting mixture was further stirred at -78 °C for 16 h. The reaction was quenched by addition of MeOH (0.1 ml) and the mixture was allowed to reach rt. Then, saturated aqueous NH_4Cl solution (2 ml) was added to the mixture. The organic phase was separated, and the resulting aqueous layer was extracted with CH_2Cl_2 (3 x 2 ml). The organic layers were combined and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, pentane/Et_2O 20:1) to afford ***syn*-11a** (23%, 10.5 mg) as a colorless oil. $[\alpha]_D^{20}$ = + 6.8° (c = 0.5 in $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.67 (m, 4H), 7.44 – 7.33 (m, 6H), 5.85 (ddd, *J* = 17.0, 10.5, 9.1 Hz, 1H), 5.04 – 4.92 (m, 2H), 3.79 – 3.70 (m, 2H), 3.54 – 3.48 (m, 1H), 3.36 (dd, *J* = 10.4, 2.1 Hz, 1H), 2.46 – 2.36 (m, 1H), 1.67 (ddd, *J* = 16.9, 6.6, 3.8 Hz, 1H), 1.38 (s, 6H), 1.06 (d, *J* = 6.1 Hz, 3H), 1.05 (s, 9H), 0.70 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.9, 135.8, 129.4, 127.5, 114.7, 112.9, 97.6, 75.4, 65.7, 39.5, 32.0, 29.9, 26.8, 19.4, 19.3, 18.0, 11.5. HRMS (ESI+, *m/z*): Calcd for $C_{28}H_{40}O_3SiNa$ [M+Na$^+$]: 475.2639, found: 475.2630.

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